EXTENDED REPORT

Non-arteritic anterior ischaemic optic neuropathy is nearly systematically associated with obstructive sleep apnoea

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Aim: To evaluate newly diagnosed non-arteritic anterior ischaemic optic neuropathy (NAION) patients for the existence of an associated sleep apnoea syndrome.

Methods: Newly identified NAION patient underwent polysomnography. The prevalence of sleep apnoea in NAION patients was compared to the prevalence previously found in the general population. Hypertension, diabetes, hyperlipidaemia, and atheromatous lesions of carotid vessels as classic risk factors associated with NAION were also identified.

Results: 27 consecutive newly diagnosed NAION patients (18 men and nine women, mean age 65 (SD 8) years, body mass index 27.2 (3.8) kg/m^2) were included in the study. 24 of these 27 NAION patients (89%) exhibited a sleep apnoea syndrome (respiratory disturbance index: 37.2/h (SD 18.3/h). Risk ratio for a NAION patient to have sleep apnoea was 4.9 compared to the general population ($p<0.001$). Sleep apnoea was 1.5–2-fold more frequent than the rate of the other identified risk factors typically associated with NAION (hypertension, diabetes).

Conclusions: Sleep apnoea is the most frequent disorder associated with NAION and should be screened in this population. At least a questionnaire related to obstructive sleep apnoea symptoms and assessment of sleepiness should be systematically proposed to patients with NAION.

Non-arteritic anterior ischaemic optic neuropathy (NAION) is a severe disease generally leading to definitive visual loss,[1] and is the most common acute optic neuropathy in the elderly, with an incidence from 2.3 to 10.2 per 100 000 people aged 50 years and older.[2 3] The pathophysiological mechanisms are not fully identified even if cardiovascular risk factors, mainly hypertension and diabetes, and mechanical factors (cup to disc ratio) have been reported. These pathological conditions favour changes in the structure or function of the microcirculation and autoregulation at the optic nerve head level. However, patients with controlled hypertension and diabetes still have NAION and, except for a promising preliminary study showing levodopa benefits in the treatment of recent onset NAION,[4] there is no established treatment for the disease.

In approximately 30% of patients, following the initial onset of acute visual loss, the visual function may continue to deteriorate over several days to weeks.[1 5] The recurrence rate of NAION in the ipsilateral eye is estimated to 6.4% (median follow up period of 3.1 years from first onset)[6] and NAION may develop in the fellow eye in 14% to 24% of cases (mean follow up period of 5 years).[7–9] The possible progression of the disease, at the acute stage or after the ischaemic event (recurrence) and the occurrence of sequential bilateral disease suggests that important risk factors have not been identified and should be taken into account for optimal management of the disease.

A prospective study in 17 patients[10] has suggested a possible association between sleep apnoea and NAION. Obstructive sleep apnoea (OSA) is an independent risk factor for hypertension,[11] insulin resistance,[12] and haemostatic abnormalities.[13] In addition, OSA is associated with acute surges in blood pressure,[14] endothelial dysfunction,[15] and an increase in the incidence of carotid atheromatous plaques.[16] These OSA related vascular changes might contribute to local ischemia/hypoxia at the optic disc level.

Taking into account the potential pathophysiological links between OSA and NAION, we designed a prospective study, systematically evaluating newly diagnosed NAION patients for the existence of sleep apnoea, and other risk factors.

METHODS

Design

Patients with NAION

The study was prospective, involving 27 consecutive patients referred to a tertiary centre for a suspected diagnosis of NAION (see criteria below). The prevalence of sleep apnoea was assessed by overnight laboratory polysomnography (see below). This study followed the tenets of the Declaration of Helsinki and informed consent was obtained from the subjects after explanation of the study.

Comparison of prevalence rates

The prevalence of OSA in the NAION population was compared to previously published data from the general population.[17]

Criteria for NAION diagnosis and severity evaluation

NAION diagnosis was established when the following items were present:

- A complaint of sudden onset of painless visual loss that affect visual acuity and/or visual field.[2] Various patterns of visual field defects are commonly found (peripheral scotomas, altitudinal, inferior arcuate, inferior quadrantic central or total visual field losses),[1] and may occur in the presence of preserved visual acuity.
- Diffuse or sectoral optic disc oedema on optic disc examination.[1] The oedematous area could be mildly pale

Abbreviations: BMI, body mass index; FN, false negative; FP, false positive; NAION, non-arteritic anterior ischaemic optic neuropathy; OSA, obstructive sleep apnoea; RDI, respiratory disturbance index; RR, risk ratio; TST, total sleep time

Table 1 Ocular data

Patients	**N = 27**
Bilateral disease	48%
Left unilateral disease	19%
Right unilateral disease	33%
Affected eyes	**N = 40**
Vertical disc diameter (mean (SD), mm)	1.8 (0.17)
Cup to disc ratio	0.21 (0.09)
Mean deviation (mean (SD), dB)	−22.3 (9.2)
VA ⩽20/200	40%
VA >20/200 and ⩽20/40	30%
VA >20/40	30%

or hyperaemic. Focal nerve fibre layer haemorrhages could also be identified.

The diagnosis of sequential bilateral NAION was documented when patients presented with all the above criteria of NAION in one eye and reported previous loss of vision and visual field defect in the other eye and exhibited optic disc pallor on examination.

One patient was excluded because of giant cell arteritis.

Visual acuity was assessed and visual field testing was systematically performed (Humphrey automated field analyser 30–2). For every patient, false positive (FP) and false negative (FN) stimuli were randomly proposed during the test. The validity of visual field results was accepted only when less than 30% of FN or FP and less than 20% of fixation losses were identified. Results were expressed as the value of mean deviations. In patients with visual acuity impairment too severe to allow accurate visual field testing, the mean deviation was arbitrarily scored at −34 dB. This value corresponds to the maximum value obtained in systematic non-response for every point throughout the visual field. This allowed assignment of results to the more severely affected patients.

Photographs of the optic disc were taken at the 30 degree setting. The vertical optic disc diameter and the cup to disc ratio were measured. Keratometry readings and spectacle refraction were used to correct for ocular magnification using a Littman algorithm.[18 19]

Sleep studies

Before overnight polysomnography, a questionnaire about OSA related symptoms and particularly measurement of subjective sleepiness by the Epworth sleepiness scale (normal values less than 10)[20] was assessed. Polysomnography was performed as previously described.[21–24]

Table 2 Symptoms and polysomnographic data

Clinical symptoms	
Epworth sleepiness score (mean (SD))	7 (5)
Reported snoring (%)	53
Nocturia (%)	50
Sleep study	**Mean (SD)**
Total sleep time (TST) (min)	363 (78)
Stage 1–2 (% of TST)	73 (12)
Stage 3–4 (% of TST)	8 (7)
REM (% of TST)	19 (9)
Respiratory disturbance index (RDI) (nb per hour of sleep)	37.2 (18.3)
Nocturnal minimal oxygen saturation (%)	83 (8)
Nocturnal mean oxygen saturation (%)	93.5 (1.8)
Time spent under 90% of SaO_2 (% of TST)	8 (15)

Others risk factors than sleep apnoea associated with NAION

All patients confirmed as having NAION underwent multiple clinical measurements of arterial blood pressure, Doppler assessment of brachiocephalic arteries, a cephalic resonance magnetic imaging, and biological assays for sedimentation rate, C reactive protein, fasting glucose and cholesterol. Tobacco consumption was recorded. The presence of giant cell arteritis was evaluated and a temporal artery biopsy was systematically obtained.

Statistical methods

All continuous variables are described by mean (SD). Normality was verified by skewness and Kurtosis tests. Means were compared by Student's *t* test or Mann-Whitney test (if data were not normally distributed). Prevalence of sleep apnoea in the NAION population and in the general population has been compared using Fisher's exact test. Significance was accepted for $p<0.05$.

RESULTS

Patients

Twenty seven consecutive newly diagnosed NAION patients (18 men and nine women, mean age 65 (8) years (range 44–78), body mass index (BMI) 27.2 (3.8) kg/m^2) were included in the study. Table 1 summarises ocular data and underscores the severity of NAION. Nearly half of the patients presented with sequential bilateral disease. Disease severity was noted, as a mean deviation of visual field above –20 dB for the whole group and visual acuity less than 20/200 in 40% of the cases.

Prevalence of sleep apnoea associated with NAION

NAION was nearly always associated with sleep apnoea; 89% of the patients had an apnoea-hyypopnoea index of more than 15 per hour of sleep. Table 2 shows clinical symptoms related to sleep apnoea and polysomnographic variables. The severity of sleep apnoea was significantly lower in women than men (27.6 (14.5) *v* 42.0 (18.5) respectively, $p = 0.05$). Table 3 reports the prevalence rates and the relative risk ratio (RR) for a NAION patient to have sleep apnoea compared to subgroups of subjects matched for sex, age, and quartiles of BMI in the general population. RR for a NAION patient to have sleep apnoea was 4.9 compared to subjects in the general population ($p<0.001$). The RR was higher in women (RR: 8.1) and for quartile I of BMI (RR 8.6).

Other risk factors associated with NAION

The prevalence rate of sleep apnoea was 1.5–2-fold more frequent than the rate of other identified risk factors classically associated with NAION (that is, hypertension, diabetes, etc) (table 4). Sleep apnoea was the only identified associated risk factor in 11% of patients. Vertical optic disc diameter were within normal for all NAION patients (mean 1.8 (0.17) mm, range 1.5–2 mm, table 1) and all patients exhibited a small cup to disc ratio (mean 0.21 (0.09), ratio <0.4 in all patients).

Treatment for sleep apnoea

Sleep apnoea was considered as severe enough by trained sleep physicians to warrant nCPAP treatment in 70% of the cases (n = 19). Treatment decision was based either on an AHI >30/h or an AHI from 15–30/h in association with a severe sleepiness or an associated cardiovascular morbidity. For the other five moderate sleep apnoea patients, weight loss and positional treatment were prescribed.

Table 3 Relative risks of having NAION

Total sample	Young *et al*[16] (n = 5615) AHI⩾15* No (Prevalence)	Current study (n = 27) AHI⩾15* No (Prevalence)	Relative risk	Lower 95% CL	Upper 95% CL
All population	1011 (18%)	24 (89%)	4.9	4.2	5.7
Sex					
Men	662 (25%)	16 (89%)	3.6	3.0	4.2
Women	326 (11%)	8 (89%)	8.1	6.3	10.5
Body mass index (BMI) (kg/m^2)†					
Quartile I	140 (10%)	6 (86%)	8.6	6.4	12.7
Quartile II	182 (13%	5 (71%)	5.5	3.4	8.9
Quartile III	239 (17%)	10 (100%)	5.9	5.2	6.6
Quartile IV	449 (32%)	3 (100%)	3.1	2.9	3.4
Age					
50–59 years	264 (16%)	4 (57%)	3.6	1.9	7.0
60–69 years	317 (19%)	10 (100%)	5.3	5.0	6.0
70–79 years	299 (21%)	9 (100%)	4.8	4.3	5.3

*Apnoea + Hypopnoea Index.
BMI quartiles: quartile I: women: 15.9 to 24.3; men: 16.7 to 25.3; quartile II: women: 24.4 to 27.5; men: 25.4 to 27.9; quartile III: women: 27.6 to 31.6; men: 28.0 to 30.8; quartile IV: women: >31.6; men: >30.8.

DISCUSSION

In a sample of 27 consecutive patients with NAION, OSA syndrome was an associated disorder in 89% of the cases. In NAION patients, the relative risk of having OSA was about fivefold the risk in the general population and eightfold in women and lean subjects. The rate of sleep apnoea was 1.5–2-fold more frequent than the occurrence of other risk factors classically associated with NAION.

Prevalence of associated OSA in NAION

Only one carefully performed study has examined the association between OSA and NAION.[10] Mojon *et al*[10] studied 17 consecutive NAION patients and found a 71% prevalence of sleep apnoea. In this previous study, measurement of airflow during sleep was based on thermistors that might have led to underestimate subtle respiratory events which are common in moderate sleep apnoea. Mojon *et al*[10] reported only two women among 17 patients, whereas the prevalence rate of NAION is about the same in men and women.[5] Furthermore, OSA related symptoms were not clearly reported in this previous study. The present study, using more sensitive tools for OSA diagnosis (that is, nasal pressure), found, as expected, a larger prevalence rate of associated sleep apnoea (89%). No bias at inclusion was expected that can explain the prevalence rate we found. The referring doctors were not aware of the study. NAION patients were hospitalised in our reference centre. Moreover, as stated in the results, the majority of patients did not complain about any sleep disturbance and the diagnosis of OSA was unpredictable based on clinical presentation. Our results confirm data from Mojon *et al* and provide additional information in terms of symptoms and prevalence rate in women with NAION. Finally, the results of both studies are robust enough to consider OSA as a risk factor when evaluating a new case of NAION. In the general population, the admitted maximum prevalence of OSA is about 20% depending upon factors such as sex, age, or obesity.[17] We have identified subgroups in the general population comparable with our group of patients for age, sex, and quartiles of BMI.[17] Even, when comparing with these appropriate controls, the relative risk of OSA among NAION patients remained significantly higher.

Table 4 Risk factors related to NAION

	N = 27
Hypertension	59%
Diabetes	37%
Dyslipidaemia	44%
Atherosclerotic lesions of carotid arteries (n = 23)	30%
Current or previous smoking (n = 24)	46%

OSA as the most frequent disorder associated with NAION

The largest population of NAION patients in whom risk factors have been systematically identified and reported consists of 406 patients included in the Ischemic Optic Neuropathy Decompression trial.[5] This group of patients was similar to our study population, with a rate of hypertension and diabetes mellitus of 49% and 26%, respectively.[5] Taking into account data from Mojon *et al*[10] and our data, OSA is thus the most frequent disorder associated with NAION. On the other hand, sleep apnoea is known to generate hypertension in a dose-response fashion and independently of other confounding factors.[11] Sleep apnoea is also associated with an increased occurrence of insulin resistance, even in lean subjects,[12] and leads to increase in carotid wall thickness.[16] Thus, part of the hypertension, diabetes, and atheromatous lesions of the carotid vessels that we found in our population might have been related to, or aggravated by, sleep apnoea .

Pathophysiology of NAION and potential mechanisms underlying the association between OSA and NAION

NAION is related to transient or sustained hypoperfusion of the optic nerve. The main mechanism associated with the disease is thus an acute or subacute ischaemia of the head of the optic nerve. This blood flow reduction depends on several factors including variations in blood pressure, increases of intraocular pressure, thus influencing vascular transmural pressure, local vasculopathy, and impairment in blood flow autoregulation.[25]

Both acutely and chronically, OSA will impact on all these factors. Acutely, in response to abnormal respiratory events, blood pressure oscillates with hypotension episodes during apnoeas and repeated peaks of hypertension at resumption of ventilation.[26] Chronically, the desaturation reoxygenation sequence, a typical pattern coupled with most respiratory events, leads to oxidative stress with production of reactive oxygen species and promote vascular endothelium damage.[27–30] Moreover, vascular endothelial growth factor, which is essential

for angiogenesis[31] and endothelin-1, a long acting vasoconstrictive substance,[32] have also been reported in increased serum concentration in OSA patients. Abnormalities in coagulation have been recently described in OSA.[13 33] Studies assessing vascular patency in NAION, and having documented atherosclerosis as a contributing factor, are lacking. Pathophysiological studies seem to indicate transient hypoperfusion that can be favoured in sleep apnoea patients by all the functional vascular changes described above and associated with sleep apnoea.

Conclusion

In our study, almost all subjects with NAION had sleep apnoea syndrome. Several pathophysiological mechanisms common to both conditions may explain this strong association. OSA appears as more frequent than other usual risk factors and is the only risk factor in a significant proportion of NAION patients. A specific investigation for the presence of OSA should then be proposed to every newly diagnosed NAION patient. The impact of sleep apnoea treatment on the evolution of NAION remains to be studied.

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